T-cell ALL in Childhood and Adolescence

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ALL in Childhood (Background)

- Most common pediatric malignancy
- 25% of cancer diagnoses
- ALL: AML (< 15 yrs. of age) 4.8:1
- Peak age incidence 2-6 yrs.
- > 3,000 cases/yr. U.S. (3.7/100,000)
- Gender/Racial Variance

ALL-Classification

- Immunophenotypic
  - B-cell Precursor (early pre-B/pre-B/ “common” B-cell) 85%
  - T-cell 15%
- Morphologic (FAB)
- Cytogenetic/Molecular genetic

Immunophenotypic Classification

B-Lineage ALL *(CD19+/CD22+)*		**T-Lineage ALL** *(CD3+ c/s)*	
▪ early pre-B *(pro-B)* (BI)		▪ pro-T (TI)	CD7+
▪ common (BII)	CD10+	▪ pre-T (TII)	CD2+ and/or CD5+/CD8+
▪ pre-B *(pro-B)* (BIII)	cIgM+	▪ Cortical (TIII)	CD1a+
▪ B (BIV)	c/m kappa or lambda	▪ Mature T (TIV)	CD3+ CD1a-

Prognostic Factors in Childhood ALL

- Age
- WBC at Dx.
- Early response to therapy/MRD
- Leukemic burden (Mediastinal mass/massive hepatosplenomegaly
- Immunophenotype (?)
- Cytogenetics: t(9,22) t(4;11) t(12;21)

(BCR/ABL) (MLL/AF4) (TEL/AML-1)

Clinical Features Associated with T-cell ALL

- Age/Gender: Males ≥ 15yr of age
  - Never ≤ 1yr of age
  - Rare 2-5yr of age (<5%)
- Mediastinal mass
- Hyperleukocytosis (WBC > 100,000)
- Massive hepatosplenomegaly

Immunologic Characterization of T-cell ALL

N.A. classification		EGIL* classification	
Immunologic subgroup	**Immunophenotypic profile**	***Immunologic subgroup***	**Immunophenotypic profile**
▪ T-lineage ALL	CD7+/cyCD3+/ CD22-/MPO-	▪ T-lineage ALL	Cytoplasmic/ surface CD3+
▪ Pre-T	sCD3-/CD5-/CD1-/CD4-/CD8-/CD10-	▪ T-I (pro-T)	CD7+
▪ Early-T	sCD3/CD5+/CD1-/CD4-/CD8±/ CD10-	▪ T-II (pre-T)	CD2+ and/or CD5+ and/or CD8+
▪ Common-T	sCD3/CD5+/CD1±/ CD4±/CD8±/ CD10±	▪T-III (cortical T)	CD1a+
▪ Late-T	sCD3/CD5+/CD1-/CD4+ or CD8+/CD10-	▪T-IV (mature T)	Surface CD3+, CD1a-
		▪α/β (group a)	TCR α/β+
* European Group for the Immunological Characterization of Leukemia		▪γ/δ (group b)	TCR γ/δ+

Immunophenotype: T-cell ALL

- > 25% of cases – profile not concordant with normal thymocyte differentiation
- Degree of maturation – not prognostic
- Level of specific antigen expression (CD5, 3, 2, 4, 8) – not prognostic

Treatment of ALL

- Risk-based treatment strategies
  - Standard
  - High
- Induction/Consolidation (CNS directed) /Delayed Intensification/Maintenance
- Subtle differences in purine salvage metabolism T-cell vs. B-cell
- Stem Cell Transplantation-Very High Risk/Relapsed
- Targeted therapy: Immunotoxins

Immunodeficiency and ALL

- Wiskott-Aldrich Syndrome*
- Ataxia Telangiectasia
- Congenital hypogammaglobulinemia
- Solid organ/BM Tx-chronic immunosuppression

*Characteristically B-cell lymphoproliferative disorder

Cytogenetics in T-cell ALL

- Normal (20-25%)
- Hypodiploid (3%)
- Hyperdiploid (4%)
- 6 q deletions (16%)*
- 9p abnormalities [*p16/p15 (9p21)*] (14%)*
- 14 q abnormalities (11%)

*Not T-cell specific

T-cell Receptor Gene Abnormalities

- t (10;14) (q24; q11) (7-14%)
- t (8;14) (q24; q11)
- t (11;14) (p15; q11) (p13; q11)
- t (7;9) (q34; q34)

TCR-α + δ – 14q11
TCR-β – 7q32-36
TCR-γ – 7p15

TAL1 Gene Rearrangements

- TAL1 (TCL5, SCL) – 1p33
  - Only 3% detected with cytogenetics t(1;14)(p33;q11)
- Transcriptional activation of TAL1
  - 30% interstitial deletion – SIL
  - (SCL – interrupting locus) fusion
- Prognostic significance?